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PHARMACEUTICAL COMPOSITION FOR  
THE TREATMENT OF SYNDROM X OF REAVEN

The present invention relates to a pharmaceutical composition comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin, for the treatment of syndrome X of Reaven (also called "Hyper Insulinemia syndrome" or "The Deadly Quartet").

Somatostatin and its analogs, e.g. octreotide, are known for the treatment of the reduction of the secretion of Insulin caused by insulimomas. Moreover, they are known for the treatment of certain tumors, gastrointestinal diseases, etc. However, their effectivity for the reduction of the resistance to insulin has so far not been known.

It is also known that Diazoxide, Cyclothiazide and Metformin achieve the reduction of the resistance to Insulin. Moreover, it is known that Metformin is used in the treatment of Diabetes and reduces risk factors in cardiovascular diseases in NIDDM.

Diazoxide, Cyclothiazide and Metformin have the following formulae:

- a. Diazoxide: 7-chloro-3-methyl-2,4,1,2,4-benzothiadiazine 1,1-dioxide.
- b. Cyclothiazide: 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
- c. Metformin: N,N-Dimethylimidodicarbonimide diamide.

However, those compounds have so far not been known for the treatment of the risk factors of syndrome X of Reaven.

Syndrome X includes, inter alia, the following risk factors:

- a. excessive blood pressure;
- b. dislipidemia, i.e. increase of the amount of Triglycerides in the blood, reduction of the amount of HDL and increase of the amount of LDL;
- c. excessive blood

coagulation due to Plasminogen Activator Inhibitor-1 (PAI-1) increased in the blood; d. central obesity; e. Glucose intolerances - from occult Diabetes to overt Diabetes f. increase of Insulin in the blood, i.e. the pancreas secretes more Insulin in order to overcome high Insulin resistance.

All the risk factors of syndrome X of Reaven are, inter alia, caused by a high resistance to Insulin. Thus, apparently said symptoms could be treated simultaneously if there would be a reduction to the resistance to Insulin.

Said risk factors either separately but mostly in combination are decisive factors in the appearance of Ischemic Heart disease, e.g. Angina Pectoris, Myocard Infarct; Cerebral Vascular Diseases and the like.

Until now, all said risk factors had to be treated separately as there was no pharmaceutical composition which could treat simultaneously all of them. However, said separate treatments are not always effective as very often the treatment of one risk factor severs the condition of another risk factor. It has therefore been desirable to find a pharmaceutical composition which can treat simultaneously all the various risk factors which are included in syndrome X of Reaven.

We have now found that due to the fact that the reduction of the resistance to Insulin can be achieved by administering a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin, said treatment may enable the treatment of all risk factors of syndrome X of Reaven simultaneously.

The present invention thus consists in pharmaceutical preparations for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.

The present invention also comprises the use of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined),

cyclothiazide or one of its analogs (as herein defined) and metformin in the preparation of a pharmaceutical preparation for the treatment of the risk factors of syndrome X of Reaven.

Analogues of somatostatin in connection with the present invention mean any analog compound of somatostatin which biologically activate one or more somatostatin receptors. Said receptors cause the reduction of the resistance to Insulin and thus enable the combined treatment of all risk factors of syndrome X of Reaven and are thus effective in primarily & secondary preventing and/or treating Ischemic Heart disease, such as, Angina Pectoris, Myocard Infarcts ; Cerebral Vascular Diseases, etc.

As receptors there should be mentioned, inter alia, the following human somatostatin receptors, which are described in Steven W.J. Lamberts, et al. 1996. Octreotide.. The New England Journal Med. Jan. 25. pp. 246-54. These receptors are:

1. hSSTR1

Present in the brain, lung, stomach, jejunum, kidneys, liver and pancreas. It is located on chromosome 14q13.

It has 391 amino acids and its formula is given in Yamada et. al., Biochemical and Biophysical Research Communications, 1993, Vol. 195, No. 2., pages 844-852.

2. hSSTR2

Present in the brain and in the kidneys, It is located on chromosome 17q24. It has 369 amino acids and its formula is given in Yamada.

3. hSSTR3

Present in the brain and in the pancreas. It is located on chromosome 22q13.1. It has 418 amino acids and its formula is given in Yamada.

4. hSSTR4

Present in the brain and in the lung. It is located on chromosome 20. It has 388 amino acids and its molecular weight is 41,867. Its formula is given in Yamada.

5. hSSTR4

Present in the brain, heart, adrenal glands, placenta, pituitary, small intestines and skeletal muscles. It is located on chromosome 20p11.2. It has 364 amino acids,

its molecular weight is 39,176 and its formula is given in Yamada.

All receptors have common features:

1. They have a similarity in the configuration in the seven areas which do extend out of the membrane TM1....TM7)
2. Asp-Arg-Tyr at the end of the NH -terminal of the second loop which is in the cell.
3. Aspartic acid (Asp) is located in the third loop outside the cell.

The receptors which are especially important in reducing the Insulin resistance are receptors 2 and 5, also but less receptor 3. Receptors 1 and 4 are less important in this respect.

The use of somatostatin is not always satisfactory as it is effective only for a short time. Therefore the use of Octreotide, the most known analog of somatostatin or of another long acting Somatostatin, is preferred.

The analogs of somatostatin should comprise the chain D-Trp-Lys. Said chain constitute the critical core of the active analogs and is essential for the activation of the receptors.

Most analogs comprise the chain Phe-D-Trp-Lys.

Many analogs comprise the chain Phe-D-Trp-Lys-Thr being present in positions 7 - 10 of Somatostatin 14.

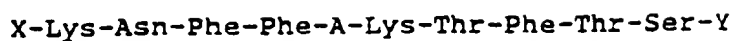
Suitable analogs of somatostatin being part of the pharmaceutical composition according to the present invention are, for example, :

1. Octreotide.
2. Vapreotide.
3. Lanreotide.
4. Cyclopeptide somatostatin analogues selected among :
  - Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
  - Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
  - Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
  - Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
  - Cyclo[Pro-Phe-D-Trp-Lys- $\beta$ -aminobutyric-Phe]
  - Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
  - Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
  - Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]

- Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a))  
 Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]  
 Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]  
 Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-  
 Tyr-Thr-Ser] [SEQ ID NO 1] (Ahep = (b))  
 Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]  
 Cyclo[Ahep-Phe-D-Trp-Lys-Thr]  
 Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]  
 Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)] (Ahex = (c))  
 Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)] (Aoct = (d))  
 Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]
- (a) Bzl = benzyl  
 (b) Ahep = 7-aminoheptanoyl  
 (c) Ahex = 6-aminohexanoyl  
 (d) Aoct = 8-amino-octanoyl;
5. D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol
  6. D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH<sub>2</sub> (Nal = (1))
  7. D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH<sub>2</sub>
  8. D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH<sub>2</sub>
  9. D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH<sub>2</sub> (Abu = (2))
  10. D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH<sub>2</sub>
  11. D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH<sub>2</sub>
  12. c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3))
  13. D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub> (Cpa = (4))
  14. D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>
  15. D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>
  16. D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>
  17. D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH<sub>2</sub>
  18. D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH<sub>2</sub>
  19. D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH<sub>2</sub>
  20. D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>2</sub>
  21. D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH<sub>2</sub>

- (1) Nal L-3(2-naphthyl)alanine  
 (2) Abu L- $\alpha$ -amino-n-butyric acid  
 (3) Ahep 7-aminoheptanoic acid  
 (4) Cpa L-p-chlorophenylalanine

## 22. Polypeptides of the formula:



wherein A is L- or D-Trp,

X is H-(Aeg)<sub>m</sub>-Cys- or H-(Aeg)<sub>m</sub>-Ala-Gly-Cys-,

Y is -Cys-(Aeg)<sub>n</sub>-OH or

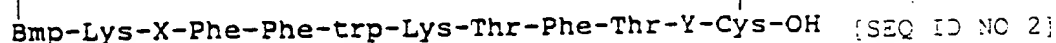
X and Y taken together are a 2-aminoethyl-glycyl group in the ring position and

m and n are 0, 1, 2, provided that

m and n are at least 1,

and their cyclic disulfide derivatives.

## 23. A peptide of the formula:



3    4    5    6    7    8    9    10    11    12    13    14

in which

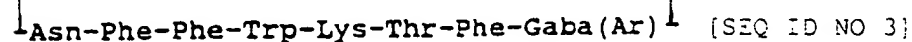
Bmp represents the desaminocysteine radical,

X represents Asn,

trp represents D-Trp that may be substituted in the benzene ring by a halogen atom, and

Y represents the radical of an alpha-(lower alkyl)amino-(lower alkyl)-carboxylic acid having a minimum of 4 and a maximum of 8 carbon atoms, in which the two lower alkyl radicals can be connected to one another with a single C-C bond, an oxygen atom or a sulphur (II) atom.

## 24. Cyclic octapeptides of the formula



5    6    7    8    9    10    11    12

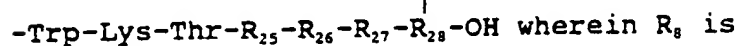
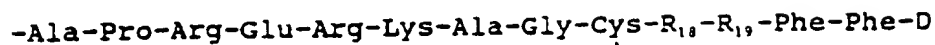
in which

Trp represents L-Trp or D-Trp, in which the benzene ring may be substituted by a fluorine atom, and

Gaba(Ar) represents the residue of a -aminobutyric acid substituted by a cyclic hydrocarbonyl radical Ar selected from the group consisting of cyclohexyl; phenyl optionally substituted by halogen, nitro or phenoxy; and naphthyl

optionally substituted by halogen.

25. A compound of formula

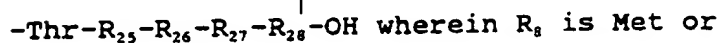
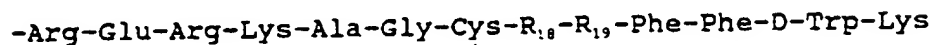


Met or Leu,  $R_{18}$  is Lys or des  $R_{18}$ ,  $R_{19}$  is Asn or

des  $R_{19}$ ,  $R_{25}$  is Phe or Tyr,  $R_{26}$  is Thr or des

$R_{26}$ ,  $R_{27}$  is Ser or D-Ser and  $R_{28}$  is D-Cys or Cys.

26. A compound of formula

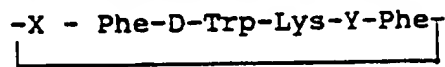


Leu,  $R_{18}$  is Lys or des  $R_{18}$ ,  $R_{19}$  is Asn or des

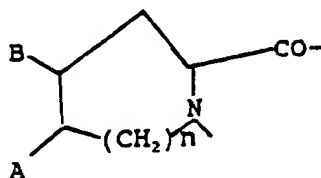
$R_{19}$ ,  $R_{25}$  is Phe or Tyr,  $R_{26}$  is Thr or des  $R_{26}$ ,

$R_{27}$  is Ser or D-Ser and  $R_{28}$  is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

27. A cyclic hexapeptide of the formula



in which X represents the radical of an L-aminoacid of the formula



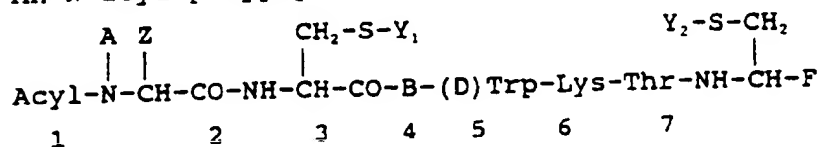
in which A and B are identical or different and denote alkyl

having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms,

n denotes 0 or 1, and

Y represents an aliphatic or aromatic L-aminoacid the side-chain of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

28. An N-acyl-polypeptide of formula,



wherein

"Acyl" is a group of formula  $\text{R}^{\text{I}}\text{CO-}$  wherein  $\text{R}^{\text{I}}$  is  $\text{C}_{1-20}$  alkyl or phenyl; a group of formula  $\text{R}^{\text{II}}\text{SO}_2\text{-}$  wherein  $\text{R}^{\text{II}}$  is  $\text{C}_{1-20}$  alkyl, phenyl or tolyl; a group

$\text{R}^{\text{III}}$

$\text{N-CO-}$  wherein

$\text{R}^{\text{IV}}$

$\text{R}^{\text{III}}$  and  $\text{R}^{\text{IV}}$  are each independently hydrogen

or  $\text{C}_{1-10}$ alkyl; or biotinyl,

A is hydrogen or  $\text{C}_{1-3}$ alkyl,

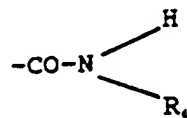
$>\text{N-CH(Z)-CO-}$  is an (L)- or (D)-phenylalanine residue optionally ring-substituted by  $\text{NO}_2$ , or an (L) or (D)-norleucine residue,

whereby

Z in  $>\text{N-CH(Z)-CO-}$  represents the remainder of said residue,

B is  $\text{-Phe-}$  optionally ring-substituted by  $\text{NO}_2$ ,

F is a group of formula



wherein  $\text{R}_4$  is hydrogen or a group of formula

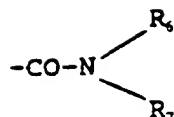
$\text{-CH(R}_5\text{)-X,}$

$\text{R}_5$  is  $\text{CH}_3\text{CH(OH)-, i-butyl or benzyl}$

X is a group of formula  $\text{-COOR}_1$ ,

$\text{-CH}_2\text{OR}_2$  or





wherein  $\text{R}_1$ ,  $\text{R}_6$  and  $\text{R}_7$  are each hydrogen or  $\text{C}_{1-3}$ alkyl, and

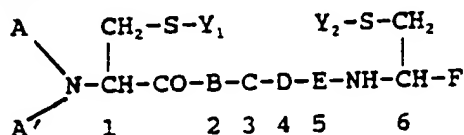
$\text{R}_2$  is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

the group  $-\text{CH}(\text{R}_3)-\text{X}$  having the (D)- or (L)-configuration, and

$\text{Y}_1$  and  $\text{Y}_2$  are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each independently have the (L)- or (D)-configuration, and with the proviso that:

- i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only.

29. A polypeptide of the formula



wherein

A is  $\text{C}_{1-12}$ alkyl,  $\text{C}_{7-10}$ phenylalkyl or a group of formula  $\text{RCO}-$ , whereby

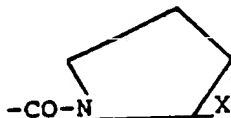
- i) R is hydrogen,  $\text{C}_{1-11}$ alkyl, phenyl or  $\text{C}_{7-10}$ phenylalkyl, or
- ii)  $\text{RCO}-$  is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or  $\text{C}_{1-3}$ alkyl,
  - b) H-Asn-, or
  - c) H-Nle-Asn-,
    - the  $\alpha$ -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- $\text{C}_{1-12}$ alkylated,

A' is hydrogen or, when A is  $\text{C}_{1-12}$ alkyl or

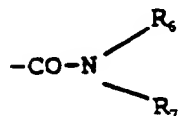
$\text{C}_{7-10}$ phenylalkyl, also  $\text{C}_{1-12}$ alkyl or  $\text{C}_{7-10}$ phenylalkyl,

- B is -Phe-optionally ring-substituted by halogen and/or  $C_{1-3}$ alkyl,
- C is -(L)- or -(D)-Trp- optionally  $\alpha$ -N-methylated and optionally benzene-ring-substituted by halogen and/or  $C_{1-3}$ alkyl,
- D is -Lys- optionally  $\alpha$ -N-methylated and optionally  $\Sigma$ -N- $C_{1-3}$ -alkylated,
- E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally  $\alpha$ -N-methylated,

F is a group of formula  $-\text{COOR}_1$ ,  $-\text{CH}_2\text{OR}_2$ ,  $-\text{CO}-\text{N} \begin{array}{l} \text{R}_3 \\ \text{R}_4 \end{array}$  or



- wherein  $R_1$  is hydrogen or  $C_{1-3}$ alkyl,
- $R_2$  is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
- $R_3$  is hydrogen,  $C_{1-3}$ alkyl, phenyl or  $C_{7-10}$ -phenylalkyl,
- $R_4$  is hydrogen,  $C_{1-3}$ alkyl or, when  $R_3$  is hydrogen or methyl, also a group of formula  $-\text{CH}(\text{R}_5)-\text{X}$ ,
- $R_5$  is hydrogen,  $-(\text{CH}_2)_2-\text{OH}$ ,  $-(\text{CH}_2)_3-\text{OH}$ ,  $-\text{CH}_2-\text{OH}$ ,  $-\text{CH}(\text{CH}_3)-\text{OH}$ , isobutyl or benzyl
- $\text{X}$  is a group of formula  $-\text{COOR}_1$ ,  $-\text{CH}_2\text{OR}_2$  or



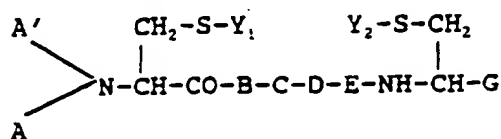
wherein

- $R_1$  and  $R_2$  have the meanings given above,
- $R_6$  is hydrogen or  $C_{1-3}$ alkyl and
- $R_7$  is hydrogen,  $C_{1-3}$ alkyl, phenyl or  $C_{7-10}$ phenylalkyl,

the group  $-\text{CH}(\text{R}_5)-\text{X}$  having the D- or L- configuration, and  $\text{Y}_1$  and  $\text{Y}_2$  are each hydrogen or together represent a direct

bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

30. A compound of formula



wherein

A is C<sub>1-12</sub>alkyl, C<sub>7-10</sub>phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C<sub>1-11</sub>alkyl, phenyl or C<sub>7-10</sub>phenylalkyl or

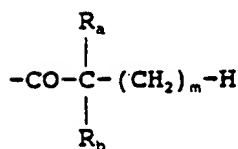
ii) RCO- is

- a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO<sub>2</sub>, NH<sub>2</sub>, OH, C<sub>1-3</sub>alkyl and/or C<sub>1-3</sub>alkoxy;
- b) the residue of a natural or synthetic α-amino acid other than defined under a) above or of a corresponding D-amino acid, or
- c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

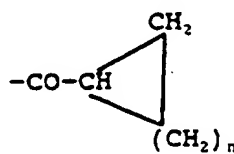
C<sub>1-8</sub>alkanoyl,

A' is hydrogen,

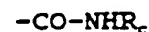
Y<sub>1</sub> and Y<sub>2</sub> represent together a direct bond or each of Y<sub>1</sub> and Y<sub>2</sub> is independently hydrogen or a radical of formulae (1) to (5).



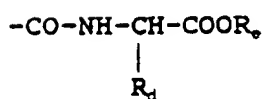
(1)



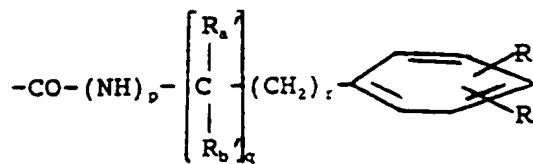
(2)



(3)



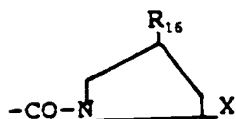
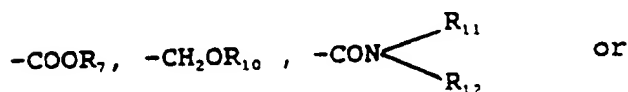
(4)



(5)

wherein

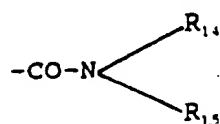
- $R_a$  is methyl or ethyl  
 $R_b$  is hydrogen, methyl or ethyl  
 $m$  is a whole number from 1 to 4  
 $n$  is a whole number from 1 to 5  
 $R_c$  is  $(C_{1-6})$ alkyl  
 $R_d$  represents the substituent attached to the  $\alpha$ -carbon atom of a natural or synthetic  $\alpha$ -amino acid (including hydrogen)  
 $R_e$  is  $(C_{1-5})$ alkyl  
 $R_a'$  and  $R_b'$  are independently hydrogen, methyl or ethyl,  
 $R_s$  and  $R_t$  are independently hydrogen, halogen,  $(C_{1-3})$ alkyl or  $(C_{1-3})$ alkoxy,  
 $p$  is 0 or 1,  
 $q$  is 0 or 1, and  
 $r$  is 0, 1 or 2,  
 $B$  is -Phe- optionally ring-substituted by halogen,  $NO_2$ ,  $NH_2$ , OH,  $C_{1-3}$ alkyl and/or  $C_{1-3}$ alkoxy (including pentafluoroalanine), or  $\beta$ -naphthyl-Ala  
 $C$  is (L)-Trp- or (d)-Trp- optionally  $\alpha$ -N-methylated and optionally benzene-ring-substituted by halogen,  $NO_2$ ,  $NH_2$ , OH,  $C_{1-3}$ alkyl and/or  $C_{1-3}$ alkoxy,  
 $D$  is Lys, Lys in which the side chain contains 0 or S in  $\beta$ -position,  $\delta$ F-Lys or  $\delta$ F-Lys, optionally  $\alpha$ -N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly. residue  
 $E$  is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue  
 $G$  is a group of formula



wherein

- $R_7$  is hydrogen or  $C_{1-3}$ alkyl,

- $R_{10}$  is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
- $R_{11}$  is hydrogen,  $C_{1-3}$ alkyl, phenyl or  $C_{7-10}$ phenyl-alkyl,
- $R_{12}$  is hydrogen,  $C_{1-3}$ alkyl or a group of formula  $-CH(R_{13})-X_1$ ,
- $R_{13}$  is  $CH_2OH$ ,  $-(CH_2)_2-OH$ ,  $-(CH_2)_3-OH$ , or  $-CH(CH_3)OH$  or represents the substituent attached to the  $\alpha$ -carbon atom of a natural or synthetic  $\alpha$ -amino acid (including hydrogen) and
- $X_1$  is a group of formula  $-COOR_7$ ,  $-CH_2OR_{10}$  or



wherein

$R_7$  and  $R_{10}$  have the meanings given above,

$R_{14}$  is hydrogen or  $C_{1-3}$ alkyl and

$R_{15}$  is hydrogen,  $C_{1-3}$ alkyl, phenyl or  $C_{7-10}$ phenylalkyl, and

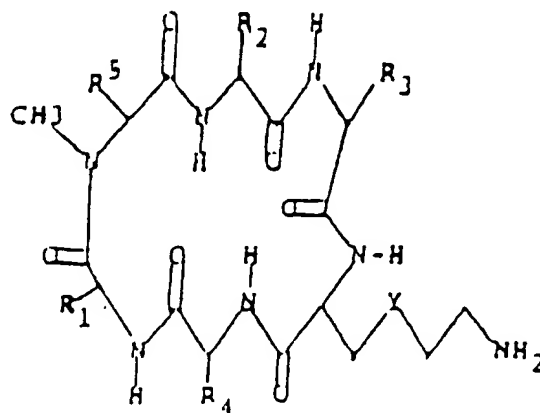
$R_{16}$  is hydrogen or hydroxy,

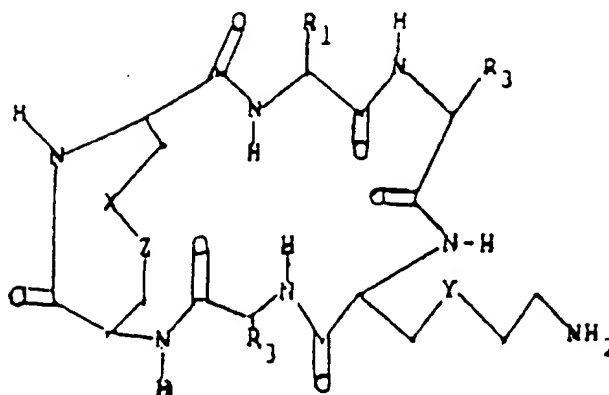
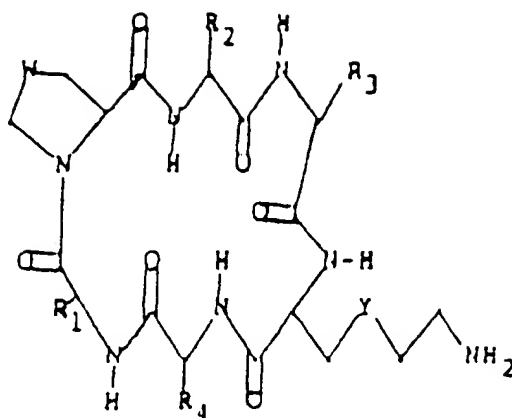
with the proviso that

when  $R_{12}$  is  $-CH(R_{13})-X_1$  then  $R_{11}$  is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues  $Y_1$  4) and  $Y_2$  4) each independently have the (L)- or (D)- configuration.

31. A somatostatin analog selected from the compounds of the following formulae





wherein

W is

one of X and Z

Y is

each of  $R_1$  and  $R_2$

S or  $(CH_2)_s$ , where s is 0, 1 or 2;

is S and the other is S or  $CH_2$ ;

S or  $(CH_2)_t$ , where t is 0, 1 or 2;

independently of the other, is  $C_{1-5}$

alkyl, benzyl, benzyl having one or two

$C_{1-5}$  alkyl, halogen, hydroxy, amino,

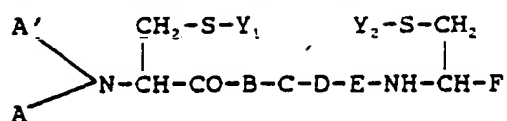
nitro, and/or  $C_{1-5}$  alkoxy substituents,

or  $C_{1-5}$  alkyl substituted with 5- or 6-

membered heterocyclic ring;

- $R_3$  is 3-indolymethyl, either unsubstituted or having  $C_{1-5}$  alkyl,  $C_{1-5}$  alkoxy or halogen substitution;
- $R_4$   $C_{1-5}$  alkyl,  $C_{1-5}$  hydroxyalkyl, benzyl, carboxy-( $C_{1-5}$  alkyl), amino ( $C_{1-5}$  alkyl) or benzyl having a  $C_{1-5}$  alkyl, halogen, hydroxy, amino, nitro and/or  $C_{1-5}$  alkoxy substituent;
- $R_5$  is  $C_{1-5}$  alkyl, benzyl, or benzyl having a  $C_{1-5}$  alkyl, halogen, hydroxy, amino, nitro, and/or  $C_{1-5}$  alkoxy substituent,

compounds of Formula



wherein

A is  $C_{1-12}$  alkyl,  $C_{7-10}$  phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen,  $C_{1-11}$  alkyl, phenyl or  $C_{7-10}$  phenylalkyl,

or

ii) RCO-is

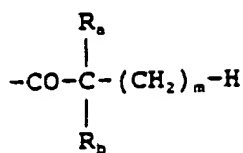
a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br,  $\text{NO}_2$ ,  $\text{NH}_2$ , OH,  $C_{1-5}$  alkyl and/or  $C_{1-5}$  alkoxy

b) the residue of a natural  $\alpha$ -amino acid other than defined under a) above or of a corresponding D-amino acid, or

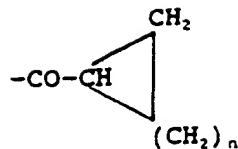
c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above, the  $\alpha$ -amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- $C_{1-12}$  alkylated,

A' is hydrogen or, when A is  $C_{1-12}$  alkyl or  $C_{7-10}$  phenylalk- also  $C_{1-12}$  alkyl or  $C_{7-10}$  phenylalkyl,

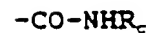
$Y_1$  and  $Y_2$  represent together a direct bond or each of  $Y_1$  and  $Y_2$  is independently hydrogen or a radical of the formulae



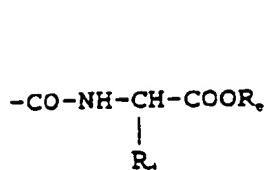
(1)



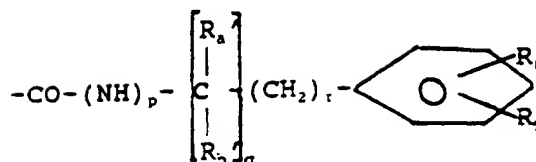
(2)



(3)



(4)



(5)

wherein  $R_a$  is methyl or ethyl

$R_b$  is hydrogen, methyl or ethyl

$m$  is a whole number from 1 to 4

$n$  is a whole number from 1 to 5

$R_c$  is  $(C_{1-6})$ alkyl

$R_d$  represents the substituent attached to the  $\alpha$ -carbon atom of a natural  $\alpha$ -amino acid (including hydrogen)

$R_e$  is  $(C_{1-5})$ alkyl

$R_a'$  and  $R_b'$  are independently hydrogen, methyl or ethyl,

$R_8$  and  $R_9$  are independently hydrogen, halogen,  $(C_{1-3})$ alkyl or  $(C_{1-3})$ alkoxy,

$p$  is 0 or 1,

$q$  is 0 or 1, and

$r$  is 0, 1 or 2,

$B$  is -Phe- optionally ring-substituted by halogen,  $NO_2$ ,  $NH_2$ , OH,  $C_{1-3}$ alkyl and/or  $C_{1-3}$ alkoxy, or naphthylalanine.

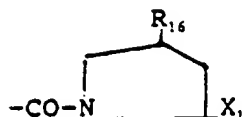
$C$  is (L)-Trp- or (D)-Trp- optionally  $\alpha$ -N-methylated and optionally benzene-ring-substituted by halogen,  $NO_2$ ,  $NH_2$ , OH,  $C_{1-3}$ alkyl and/or  $C_{1-3}$ alkoxy,

$D$  is -Lys-, ThiaLys, F-Lys,  $\delta$ F-Lys or Orn, optionally  $\alpha$ -N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,

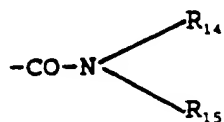
$E$  is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue



F is a group of formula  $-\text{COOR}_7$ ,  $-\text{CH}_2\text{OR}_{10}$ ,  $-\text{CON} \begin{array}{l} \nearrow \text{R}_{11} \\ \searrow \text{R}_{12} \end{array}$  or



wherein  $\text{R}_7$  is hydrogen or  $\text{C}_{1-3}$ alkyl,  
 $\text{R}_{10}$  is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,  
 $\text{R}_{11}$  is hydrogen,  $\text{C}_{1-3}$ alkyl, phenyl or  $\text{C}_{7-10}$ -phenylalkyl,  
 $\text{R}_{12}$  is hydrogen,  $\text{C}_{1-3}$ alkyl or a group of formula-  
 $\text{CH}(\text{R}_{13})-\text{X}_1$ ,  
 $\text{R}_{13}$  is  $\text{CH}_2\text{OH}$ ,  $-(\text{CH}_2)_2-\text{OH}$ ,  $-(\text{CH}_2)_3-\text{OH}$ , or  $-\text{CH}(\text{CH}_3)\text{OH}$   
 or  
 represents the substituent attached to the  $\alpha$ -carbon atom of a natural  $\alpha$ -amino acid (including hydrogen) and  
 $\text{X}_1$  is a group of formula  $-\text{COOR}_7$ ,  $-\text{CH}_2\text{OR}_{10}$  or



wherein  
 $\text{R}_7$  and  $\text{R}_{10}$  have the meanings given above,  
 $\text{R}_{14}$  is hydrogen or  $\text{C}_{1-3}$ alkyl and  
 $\text{R}_{15}$  is hydrogen,  $\text{C}_{1-3}$ alkyl, phenyl or  $\text{C}_{7-10}$ phenylalkyl, and  
 $\text{R}_{16}$  is hydrogen or hydroxy,  
 with the proviso that  
 when  $\text{R}_{12}$  is  $-\text{CH}(\text{R}_{13})-\text{X}_1$  then  $\text{R}_{11}$  is hydrogen or methyl,  
 wherein the residues B, D and E have the L-configuration,  
 and the residues in the 2- and 7-position and any residues  
 $\text{Y}_1$  4) and  $\text{Y}_2$  4) each independently have the (L)- or (D)-  
 configuration

and compounds of the following formulae

H-Cys-Phe-(D)Trp-Lys-Thr-Phe-Cys-OH

Asn-Phe-Phe-(D)Trp-Lys-Thr-Phe-Gaba

-MeAla-Tyr-(D)Trp-Lys-Val-Ph

NMe-Phe-His-(D)Trp-Lys-Val-Ala.

### 32. Somatostatin analogs

X-Cys-D-o-Trp-E-F-Cys-Y

I [SEQ ID NO 4]

X-Cys-Lys-Asn-Phe-D-o-Trp-E-F-Phe-Thr-Ser-Cys-Y

II [SEQ ID NO 5]

I, II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R<sup>1</sup>); R<sup>1</sup> = C<sub>1-6</sub>(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH<sub>2</sub>, NHR<sup>1</sup>.

33. Peptides RR<sup>1</sup>NCHR<sup>2</sup>CONHCH(CH<sub>2</sub>SR<sup>4</sup>)CO-Phe-Trp-Lys-X-NHCHR<sup>3</sup>CH<sub>2</sub>SR<sup>5</sup>  
[R = inorg. or org. acyl group, R<sup>1</sup> = H, alkyl, NCHR<sup>2</sup>CO moiety = I.

Me(CH<sub>2</sub>)<sub>3</sub>CO-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol I

or D-Phe (optionally ring substituted by halo, NO<sub>2</sub>, OH, alkyl, alkoxy); Phe, Trp, (D or L), may be ring substituted by NO<sub>2</sub>, NH<sub>2</sub>, OH, alkyl, alkoxy; Lys may be α-N-methylated and ε-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R<sup>3</sup> = CO<sub>2</sub>H, CH<sub>2</sub>OH, carbamoyl, R<sup>4</sup> = R<sup>5</sup> = H, R<sup>4</sup>R<sup>5</sup> = bond]

34. H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-X<sup>1</sup>-X<sup>2</sup>-Phe-Phe-D-Trp-Lys-Tys-Thr-X<sup>3</sup>-X<sup>4</sup>-X<sup>5</sup>-X<sup>6</sup>-OH

35. H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys  
-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

Said compounds (34 and 35) appear in Chemical Abstracts 98,  
1983 1 43839 q

36. c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

- a) R,S- $\delta$ -Bn-o-AMPA
- b) R- $\alpha$ -Bn-NMe-o-AMPA
- c) Phe-Pro

Said compounds and similar ones appear in Brex et al., Lett.  
Pept. Sci. 1995, 2 (3/4): 165-8, "Somatostatin analogs  
containing O-amino methyl phenyl acetic acid as a bridge  
unit"; and Tourwe, Lett. Pept. Sci. 1995, 2 (3/4): 182-6,  
"Conformation directed design of cyclic Somatostatin  
containing a BVI-turn mimetic".

37. H<sub>2</sub>N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-  
OH [SEQ ID NO 6]
38. H<sub>2</sub>N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-  
Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH [SEQ ID NO 7]
39. D-B-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>
40. Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>
41. D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH<sub>2</sub>
42. D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH<sub>2</sub>
43. D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>
44. D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH<sub>2</sub>
45. 3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH<sub>2</sub>
46. c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)

Aha = 7 -amino heptanoic acid.

Analogues of Diazoxide and Cyclothiazide are compounds which  
affect the receptor being adenosine 5'- triphosphate sensitive K<sup>+</sup>  
channels.

Suitable analogues of Diazoxide and of Cyclothiazide are  
indicated, for example, in a paper of Bertolino et al., appearing  
in Receptor-Channels 1993 1(4):267-78 "Modulation of AMPA/Kainate  
Receptors by Analogs of diazoxide and cyclothiazide in thin

slices of rat hippocampus". However, the analogs which may be used in the pharmaceutical composition according to the present invention are not restricted to the analogs given in said paper and any other analog having the proper properties may be used.

The pharmaceutical preparation according to the present invention may also comprise additional compounds such as compounds having an additional pharmaceutical effect, carriers, solvents, emulgators, etc.

In view of the fact that diazoxide sometimes has undesired salt and water retention, which may be relieved by certain thiazide diuretics, e.g. 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Chlorothiazide); 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Hydrochlorothiazide); 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Trichlormethiazide); or 6-chloro-3,4-dihydro-2-methyl-3[(2,2,2-trifluoroethyl)thiomethyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Polythiazide), the pharmaceutical compositions according to the present invention may comprise, in addition to Diazoxide and/or one of its analogs, as an additional compound having a pharmaceutical effect, one or more of the above thiazides or a thiazide having similar properties. Said thiazide diuretics may prevent the salt and water retention.

The present invention also comprises a method for the treatment of the risk factors of syndrome X of Reaven by applying to a patient a pharmaceutically effective dosage of a pharmaceutical preparation according to the present invention comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.

Said dosage should preferably not exceed 50 µg/kg/day of the active ingredient (calculated on Octreotide), preferably not exceeding 40 µg/kg/day. Said dosage is given in any suitable manner. It may be given as one portion once a day or even in two days or more when given in slow release form, or being divided into 3-4 dosages which are applied in equal periods of time for Octreotide, or 1 - 2 times a day for analogs with a higher t<sub>1/2</sub>.

Said dosage should preferably not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and preferably not exceed 15/mg/day in the treatment of children. The amount of Metformin applied should preferably not exceed 2.5 g/day divided into 2 - 3 portions.

Should any of the above thiazide diuretics be added the added amounts are, for example, the following:

Chlorothiazide: 500 - 2000 mg a day;  
Hydrochlorothiazide: 50 - 200 mg a day;  
Trichloromethiazide: 12.5 - 50 mg a day;  
Polythiazide: 1- 4 mg a day.

Said dosage has to be re-calculated on the basis of the analog being the active ingredient. Moreover, the exact dosages have to be adapted to the condition of the patients and to its specific properties e.g. weight, age, etc.

The composition may be administered in various manners. This depends in particular on the analog being the active ingredient. Thus octreotide is advantageously injected sub-cutaneously as a saline solution. Cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) is advantageously administered per os.

The treatment is performed, as indicated above, against the risk factors of syndrome X of Reaven, in particular against the following diseases in order to primarily and secondarily prevent and to treat:

- A. 1. Ischemic Heart diseases, e.g. Angina Pectoris and Myocard Infarcts;
2. Cerebral vascular diseases in order to prevent Transient Ischemic attack (TIA) and Cerebrovascular accident (CVA);
3. Intermittent Claudication;
4. Ischemic Bowel disease; and
5. Impotence due to a Peripheral vascular disease.
- B. Prevent excessive blood coagulation (high PAI-1 in the blood) in order to primarily prevent MI, CVA, Renal vein thrombosis, etc.
- C. Lower body weight (which is also a risk factor for high blood pressure, Glucose Intolerance, etc.)

Said diseases are mainly caused, as indicated above, by a

high resistance to Insulin.

The present invention will now be illustrated with reference to the following experiment (all injections are given into the hollow space of the Peritoneum):

60 fat male rats of the Zucker species, aged 7 weeks having an average weight of 225 g. 54 rats of same are divided into 3 groups:

Group A receives injections of Octreotide in a 0.9% NaCl saline solution in a high dosage (40 µg/kg/day);

Group B receives injections of Octreotide in a 0.9% NaCl saline solution in a low dosage (20 µg/kg/day); and

Group C the control group, receives an injection of a 0.9% saline solution. The volume of the 0.9% NaCl is identical with the volume being injected into Group A and B (At the beginning of the tests the rats have approximately the identical weight and they therefore receive the identical volume of injections).

All rats receive the same amount of Food (Pair Fed). Said amount is chosen according to the group eating the lowest amount. Thus, the influence of the drug is isolated.

The rats are located in a room changing light and darkness in order to simulate natural surroundings, as in general they eat in darkness. The rats drink water freely.

The rats are weighed twice a week. At the end of the experiment the rate change of the weight is being calculated. The amount of food eaten per week is measured and the amount eaten each day is calculated. (The influence of the Octreotide on the amount of food eaten by the rats is not checked. They eat the identical amount of food.)

Six rats are tested before the beginning of the experiment. Six rats from each group are separated after 2 weeks, 4 weeks and 8 weeks and an Intra-Peritoneal Glucose Tolerance Test (GTT 1.0g Glucose/kg BW) is performed after a fast of 12 hours during which the rats do not receive any medicament or food.

Blood is taken from the Supra-orbital sinus with slow anaesthesia with CO<sub>2</sub>.

At zero time, i.e. before the Glucose load 2 cc of blood are taken from each rat.

½ cc of blood is put into a test tube which contains Heparin

and the concentrations of Glucose and Insulin are determined;  
and

1½ cc of blood is put into a test tube which contains Na<sub>2</sub>EDTA 0.1% and the concentrations of Cholesterol, Triglycerides, HDL and LDL are determined.

At 15, 30 and 60 minutes after the Glucose load, ½ cc of blood is taken from each rat and put into a test tube which contains Heparin and the concentrations of Glucose and Insulin are determined.

After the Glucose tolerance test each tested rat "leaves" the experiment.

The materials used in the experiments:

Octreotide manufactured by Sandoz Basel.

0.9% NaCl

30% Glucose

Not sterilized food for mice and rats manufactured by Kopolk, Petach Tikva. Catalogue No. 19510. Gross energy 3,950 kCal/kg. Digestibility energy of the food in rats 3,150 kCal/kg.

The laboratory tests are performed as follows:

1. Glucose is tested by the Glucose Oxidase method in a kit of Boehringer Mannheim called Glucose GOD-Perid Method 2 x 300ml catalogue No. 124028. The test is performed on the day or the following day on which the blood is taken.

2. The Insulin is tested by the Radio Immuno Assay (RIA) by a SB INSIK-5 kit of Sorin Biomedica.

The method is performed by the general method known for the test of Insulin by said kit.

3. The total Cholesterol is tested by the CHOD-PAP method. The total cholesterol comprises VLDL + LDL + HDL. The kit with which the test is performed is manufactured by Boehringer Mannheim and the cholesterol reagent is MPA3 catalogue No. 236691 4 x 500ml.

The HDL is tested by precipitating LDL and VLDL with Heparin MnCl<sub>2</sub> and then the total cholesterol is tested. VLDL is calculated by T.G./5. LDL is calculated by the formula

$$\text{LDL} = \text{total cholesterol} - (\text{VLDL} + \text{HDL})$$

4. The Triglycerides are being tested by the peridochrom T.G. GPO-PAP method. The kit is manufactured by Boehringer

Mannheim and the reagent has catalogue No. 701904 15 x 32ml.

The data received are worked up by standard methods for this purpose. The results show that the Insulin resistance is significantly lowered, there is an increase in the level of HDL and a decrease in the level of LDL and of the Triglycerides. A decrease in the rate of weight gain of young obese rats is observed, which implies a decrease in the weight of adult obese rats.

The Insulin resistance (Insulin Sensitivity Index) is determined using the dynamic test - the Glucose Tolerance Test (GTT). An integration of the area under the curve (AUC) of Glucose and Insulin in the period of 1½ hours is measured and the determination of the ratio between them gives a good estimate of the Insulin resistance.